Genitourin Med 1989;**65**:229–234

Eminent venereologists. 1. Albert Neisser

J D ORIEL

Albert Ludwig Sigesmund Neisser was a Prussian. He was born in 1855 at Schweidnitz, a small town near Breslau. His father Moritz was a well known Jewish doctor who was devoted to his practice, and his strictness and insistence on hard work had a lifelong influence. Neisser's mother died when he was one year old, and he was brought up by his stepmother. After attending a local elementary school, he studied at St Maria Magdalena Grammar School in Breslau (where he was a classmate of Paul Ehrlich). In 1872 he became a medical student in Breslau and, apart from one clinical semester at Erlangen in Bavaria, remained there until he qualified. The University of Breslau was one of the best in Germany, and Neisser received a thorough grounding in clinical and laboratory medicine, including the new sciences of bacteriology and immunology, from teachers who included Cohnheim, Weigert, and Biermer. Like some other famous people, he was not an outstanding student, but he passed the state examinations and received an MD in 1877 with a thesis on echinococcosis. He had wanted to be a general physician, but there were no vacancies for assistants in Biermer's department of medicine, so he decided to accept a training post in the university skin clinic. In Germany, dermatology and venereology were almost invariably combined as one specialty. The skin clinic in Breslau had been founded by Kobner in 1876, but since 1878 it had been directed by Oscar Simon. In two years, Neisser had completed his basic specialist training.

For some time it had been strongly suspected that gonorrhoea was an infection caused by bacteria. Several candidate organisms had been proposed, but the suggestions had come to nothing. Neisser had been interested in microbiology as a student; he had learned from Cohn and Weigert the use of aniline dyes for staining specimens, and Koch had published his smear technique in 1877. Using these methods and a Zeiss microscope that incorporated the new Abbe condenser and an oil immersion system, Neisser embarked on his studies. In 1879, at the age of 24, he published his first and best known paper.[1] He described the identification of characteristic "micrococci" in smears, stained with methyl violet, from 35 men and nine women with purulent urethritis and from two patients with acute ophthalmia, but not in specimens from patients with syphilis or balanitis. "They are seldom seen as solitary individuals; almost always they appear as two micrococci packed close together, so that they give the observer the impression of a single

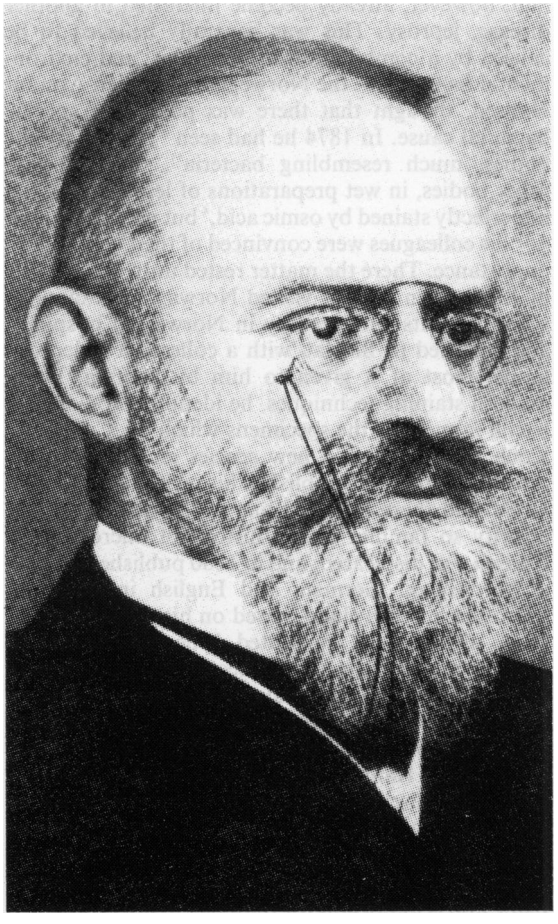

Fig. *Albert Neisser. (From W M Allen Pusey, The History of Dermatology, 1933. Courtesy of Charles C Thomas, Publisher, Springfield, Illinois.)*

Address for reprints: Dr J D Oriel, 138 Harley Street, London W1N 1AH, UK

Accepted for publication 21 April 1989

organism shaped like a figure of eight." Although his findings were soon confirmed by others, the organisms were not yet generally accepted as being the cause of gonorrhoea, and Neisser himself reserved final judgement on the matter pending successful culture and inoculation experiments. Culture proved difficult, and Neisser did not achieve it, but Koch's postulates were finally satisfied when gonococcal urethritis was induced in people inoculated with cultures by the gynaecologists von Bumm in Switzerland in 1883[2] and Wertheim in Vienna in 1891.[3] These experiments, however dubious ethically they may appear to the modern reader, established beyond doubt that the gonococcus (the name given by Ehrlich, not Neisser) was indeed the cause of gonorrhoea.

In later life Neisser would often say "What would I have been without the gonococcus?", and indeed the discovery was a brilliant beginning to his career. He had, however, already become interested in another disease, leprosy. This was generally believed to be caused by a combination of hereditary and environmental factors, but the Norwegian physician Armaur Hansen, thought that there was possibly a specific bacterial cause. In 1874 he had seen "small staff-like bodies, much resembling bacteria", together with other bodies, in wet preparations of leprous material imperfectly stained by osmic acid,[4] but neither Hansen nor his colleagues were convinced of their aetiological importance. There the matter rested until the summer of 1879, when Neisser visited Norway. He examined many patients with leprosy in Norwegian hospitals, and returned to Breslau with a collection of leprous tissue, most of it given to him by Hansen. Using modern staining techniques, he identified rod-shaped bacilli in most of the specimens which he, Cohn, and Koch thought were a new species and the possible cause of leprosy. He published his results at the end of 1879,[5] and there followed one of the disputes about priority so familiar in the history of microbiology. Hansen was displeased, and in 1880 published a paper in Norwegian, German, and English in which he reiterated his own claim, based on his experiments of 1874, although he presented little new material.[6] Neisser returned to the subject in 1881.[7] He was tactless enough to try to discredit Hansen, who had treated him with generosity during his visit, and to assert the importance of his own discoveries in comparison. Hansen had good reason to feel upset, but did not discuss the subject again until he came to write his memoirs 30 years later, when he referred to it briefly and without rancour.

The "Hansen-Neisser controversy" rumbled on for years[8] and is important for the effect it had on Neisser. As on other occasions, he was really unable to understand that his actions were open to criticism. According to his great nephew, Richter,[9] he regarded his work with the leprosy bacillus as more important than his discovery of the gonococcus, and in later life he still felt resentful that he had not received the recognition which he thought was his due. Today, Hansen appears to be the true pioneer, facing scepticism and outright opposition to his idea that leprosy was an infectious disease, as he did see the causal bacilli, however imperfect his technique. Neisser, on the other hand, with his consuming interest in bacteriology and much better laboratory methods, gave the first good description of the bacilli and their relation to the lesions of the disease. The latter was later to become the subject of a bitter dispute between Neisser and the dermatologist Unna.

Between 1880 and 1882 Neisser worked in Leipzig with Cohnheim and Weigert on various skin diseases. He had a particular interest in lupus vulgaris and its relation to tuberculosis, and he differentiated it from non-tubercular chronic dermatoses, such as lupus erythematosus and cutaneous sarcoidosis.[10] In March 1882 his teacher Oscar Simon, whom he had greatly admired, died unexpectedly of cancer of the stomach, and at the age of 27 Neisser was appointed associate professor and director of the university skin clinic in Breslau. Here his talents found their full expression. His first task was to find new premises for his department, which was housed in primitive conditions in All Saints Hospital. Thanks to Neisser's energetic fund raising, which produced generous contributions from the business community, a new purpose built clinic was opened in 1892. It was a large and imposing building, with 95 beds, extensive outpatient facilities, laboratories, lecture theatres, an animal house, a museum, and a library.[11] Apart from visits abroad, Neisser spent the rest of his professional life in Breslau. In 1883 he married Toni Kauffmann, a charming and cultivated member of a rich Jewish family. Under his leadership the university skin clinic became a major centre for clinical work, research, and training in dermatovenereology. Neisser himself made contributions to the study of many skin diseases, including anthrax, actinomycosis, psoriasis, mycosis fungoides, and vitiligo. In 1899 he confounded the German Dermatological Society, and in 1902 the German Society for Combating Venereal Disease, of which he remained secretary general until his death. Amid all this activity he also found time to build up a large private practice.

In 1899 and 1902 Neisser addressed major international conferences in Brussels. He stressed that not only syphilis but also gonorrhoea were major causes of disease and disability, and he gave the following vivid account of the results of gonococcal pelvic infection in women: "Should the infection reach the tubes, an acute febrile affection with severe attacks of pain, combined with tumour-like swelling of the tubes,

occurs which even in the most favourable cases keeps the patient in bed for weeks and requires the most careful treatment. Even after this, the condition usually is not entirely cured but leads to chronic persistent ill-health with frequent acute exacerbations. These recurrent attacks may become a danger to life, so that operative interference and removal of the collections of pus by laparotomy becomes inevitable. When both tubes are infected there is every prospect of lasting sterility."[12]

Syphilis was such an important part of nineteenth century medicine that Neisser inevitably became concerned with it. Using various formulations of mercury, he introduced Fournier's "chronic-intermittent treatment" into Germany.[9] He had been impressed by Behrer's successful use of antisera against diphtheria and tetanus, and considered the use of serum from people with syphilis for passive immunisation, and even for treatment, making the false assumption that cell free serum would contain no infective material. His experiments in this area had disastrous results.[13] In 1892 he injected subcutaneously serum from a patient with early syphilis into four female patients aged 10–24; three had skin diseases and one had gonorrhoea and condylomas. None of them developed syphilis. He then injected intravenously up to 30 ml of serum samples from patients with various stages of syphilis into four prostitutes aged 17–20, presumably with the object of keeping them under observation as "high risk" subjects to see whether any of them became immune. They all developed syphilis, however, two within a few months of the injections. Neisser stated that "immunity has not resulted from the infusions", but it seems possible that the serum may have caused two of the infections. At all events, when news of these experiments became known there was a public outcry, Neisser was accused of "maliciously inoculating innocent children with syphilis poison", and the matter reached the Prussian parliament. The criticism had several elements. He had not obtained informed consent for the experiments, there was an increasing distaste for human experimentation and the unfettered powers of university professors, and probably personal animosity because of the liberal views that Neisser had expressed in the Breslau City Council. He wrote a long, defensive, and rather unconvincing statement to justify his experiments,[13] and he was supported by many of his colleagues, but there can be no doubt that he was in the wrong. After the intervention of Friedrich Althoff, the minister responsible for science, Neisser escaped with an official reprimand and a fine. He was surprised and dismayed by this outcome and felt that his honour as a scientist had been impugned. Nevertheless, in some respects he may have been lucky. Hansen, who attempted inoculating people with leprous material, was dismissed as physician to the Bergen leprosy hospitals and never practised clinical medicine again.

If Neisser was to continue to study syphilis, he clearly had to find an animal model. In 1903 Metchnikoff and Roux had shown that chimpanzees could be infected,[14,15] and Neisser decided to use this approach in Breslau. It is said that at one time he had a colony of 200 monkeys in the grounds of his own house,[16] but they were expensive and did not thrive in the cold Silesian weather, so he decided to continue the studies in a tropical area where monkeys were easier to come by. In February 1905, accompanied by his wife and colleagues, he set out for Java, and the experimental unit was established in Batavia (now Jakarta). In May he was joined by his assistants, Halberstaedter and von Prowazek. Neisser returned to Breslau in October of that year, but he kept in close touch with the progress of the work and visited Java again from December 1906 to November 1907. All this must have been an expensive undertaking. He financed the studies from his own resources initially, but later received support from the German government and from private donations.[17]

The experimental work was performed on over 1000 monkeys of various types, and many experiments concerning the natural history of syphilis were performed. Neisser's group established the incubation period of the disease. They showed that the causal "virus" was present in the blood within a few hours of inoculation, and deduced from this that the removal or destruction of the primary chancre, a procedure often performed at the time, would not affect the subsequent course of the infection. They settled an old controversy by showing that a person treated for syphilis does not become immune to reinfection. They were unable to immunise monkeys against syphilis, and attempts to produce an effective antiserum were also unsuccessful. A full account of the enormous amount of experimental work was given in a book published in 1911.[18] It is of interest that while in Java, Halberstaedter and von Prowazek became interested in trachoma and asked Neisser's permission to perform some research into the disease. This was refused, but fortunately they went ahead with their studies, which led to the discovery of *Chlamydia trachomatis*. Their paper was not included by Neisser in the list of publications by members of the expedition that appeared at the end of his book.

While Neisser was in Java in 1905, Schaudinn and Hoffmann reported the discovery of *Treponema pallidum*.[19] At first, like many others, Neisser did not believe that this organism was truly the cause of syphilis. In a letter in June 1905 he wrote "we are still toiling with the syphilis spirilla. Here and there we find something positive, but on the whole we are more convinced than ever that these spirilla are not really

the syphilis spirilla." By the next year, after confirmatory reports by other workers (including his own team in Java), he had changed his mind. The discovery of *T pallidum* and his own experiments led indirectly to Neisser's concern with developing a serological test for syphilis. The exact sequence of events is disputed. According to Hecht,[20] who met Neisser in 1911, when Neisser returned from Java in 1906 he went to Berlin to see Wassermann, who was an old friend. Bordet and Gengou had invented the complement fixation reaction in 1901, and Wassermann had used it to try to show tuberculin in tuberculous tissue. Neisser suggested that the test might be applied to syphilis. Although he could not supply an extract of treponemes to use as antigen, he could provide the liver of an infected foetus and test and control serum samples from his monkeys. Wassermann's version, told in his obituary of Neisser, is that, although Neisser expressed dissatisfaction with the current state of syphilis serology, it was Wassermann himself who had the idea of devising a complement fixation test. Be this as it may, they agreed to begin the studies. Wassermann's and Neisser's assistants, Bruck and Schucht, prepared the material and performed the tests. These were successful with the monkey serum. In their first paper the authors said: "The practical importance of these findings is obvious . . . .it would be of the greatest diagnostic and therapeutic importance if one could regularly demonstrate syphilitic material or antibodies in the circulating blood of syphilitics."[21]

They then examined human sera; again, complement fixation was observed, although they obtained only 49 positive reactions from 257 people with "certain" syphilis.[22] In one of the disputes characteristic of research work then as now, Bruck later publicly complained that Wassermann had taken the credit for the test although Bruck had done most of the work. Neisser's role in these studies seems to have been peripheral, but in later years he often paid public tribute to Schaudinn, Metchnikoff, Roux, Wassermann, and Bruck.[23] Wassermann believed that the test was immunologically specific; in this he was mistaken, and it took several years for the problems of sensitivity and specificity to be overcome so that the "Wassermann reaction" could become clinically useful.

Neisser did not become a full professor until 1907, 25 years after he had been appointed associate professor. Prejudice and conceivably antisemitism may have been part of the cause of this long delay, though dermatovenereology was possibly not regarded as very important. The occasion, however, was marked by a *Festschrift* to which more than 60 of Neisser's students contributed original papers. In the following year William Osler heard him speak in Vienna. He wrote to a friend: "On Tuesday morning Professor Neisser of Breslau opened the discussion on "the present position on the pathology and therapy of syphilis". This was a splendid address, delivered without notes, and in a good clear voice, the subject matter being arranged in a most orderly manner."[24]

The discovery of arsphenamine (Salvarsan, or "606") by Paul Ehrlich was a turning point in treating syphilis and indeed in the history of medicine. After success with animal experiments, he gave small amounts of the drug to various clinicians for trial, including his old friend Neisser—"Albertus Maximus", as he called him. The reports began to appear in 1910. Neisser was enthusiastic. "We must advise everyone with syphilis . . . to seek the new medicine".[25] He thought that the current recommended dosage—two or three intravenous injections—might be too small, and he did not think that treatment with mercury should be abandoned, but that arsenic and mercury should be used concurrently,[23] which became the standard practice for many years.

In his later years Neisser became increasingly interested in the public health aspects of the sexually transmitted diseases, and was among the first to advocate control by the provision of public clinics, the regulation of prostitution (but by voluntary rather than coercive measures), and health education. All this activity took place at a time when many people thought the subject too disgusting even to discuss. He travelled widely and received many distinctions and awards, including the Gold Medal of the West London Medico-Chirurgical Society, which was presented to him after a lecture in 1911.[23] His incessant work as clinician, researcher, teacher, editor, and administrator, however, was tiring him. In 1911 he fell down the stairs to the cellar of his house and fractured his femur. Recovery was slow, and the leg permanently shortened. He also developed diabetes mellitus and renal calculi. In 1913 his wife, Toni, died. He never recovered from her loss, but buried himself in his work. The onset of the first world war in 1914 greatly saddened him—it was the second European war of his lifetime, and it meant separation from many of his colleagues overseas. He became very committed to programmes to control sexually transmitted disease in the German Army, which meant continuous travel despite his poor health. In the summer of 1916, although he had renal colic and a urinary infection, he attended an exhibition in Brussels. Shortly after this, while visiting Dusseldorf, he developed renal colic again. He struggled on as far as Berlin, where a calculus was removed from his bladder. Two days later, still with a draining wound, he insisted on returning to Breslau. Inevitably, infection followed, and he died of septicaemia on July 31. He was 61.

The obituaries that followed Neisser's death make clear the esteem and respect in which he was held.

Jadassohn, who was to be his successor at Breslau, contributed 53 pages to the *Archiv für Dermatologie und Syphilis*,[26] and in Britain, although the fighting of the first world war was then at its height, the *Lancet* stated in a leading article: "By the death of Professor Albert Neisser, Germany has lost one of her greatest scientists and the whole world is poorer for the loss."[27] What sort of man was he? Physically he was tall and slim, with a swarthy complexion, deep set dark eyes and, in later life, a bushy beard. Temperamentally, he had the same qualities of determination and singleness of mind as his father, and indeed as his compatriot Bismarck. He was a born leader. His contemporaries often refer to his ability to grasp essentials, matched by an iron will and inexhaustible energy.[28] He used to say "life without work would be unbearably dull", and today he would be called a workaholic. He was as meticulous in management as in research; he had a rule that all letters must be answered within 24 hours, and saw nothing wrong in expecting his junior staff to work late at night. His criticism could be harsh and abrasive, particularly in his younger days. It would not be fair to conclude from this that Neisser was simply a tyrannical professor of the old school. Those who knew him speak of his vitality, sense of humour, and personal charm.[29] These qualities made him an excellent teacher. He took a great interest in his juniors, and helped them in many ways; he used to say that fate had denied him children of his own, and that their place was taken by his students.[30] Much of Neisser's clinical work, teaching, and research was devoted to dermatology, and a generation of specialists in university departments and hospitals had been trained by him. He had a profound knowledge of literature, and he played the piano well enough to appear in public with a chamber orchestra. He loved art, and his house in Breslau was filled with paintings, sculptures, and artefacts from his visits to Java. He and his wife entertained distinguished artists including Gerhart Hoffmann, Richard Strauss, and Gustav Mahler. The marriage seems to have been exceptionally happy, and they had an adopted son.

Neisser was the first venereologist to apply scientific principles to clinical work, and he had an enormous influence on the development of the specialty. He is best remembered today for his discovery of the gonococcus. Admittedly, given the state of development of bacteriology at the time, this discovery was bound to be made, but Neisser was the one with the skill and patience to make it. The "father of the gonococcus" remained interested in gonorrhoea. He insisted on the control of treatment by microscopy of specimens rather than simple clinical examination. He strongly advocated the use of bactericidal irrigations, particularly with organic silver salts, for treating patients with gonococcal urethritis, rather than the astringents that had been used previously, which he considered harmful.

Although the prize of discovering *T pallidum* eluded him, his studies of the natural history, diagnosis, and treatment of syphilis led to a system of clinical management which, with modifications, lasted until the discovery of antibiotics. Neisser's work on gonorrhoea and syphilis are only part of his achievements that, as Harrison said in an address celebrating the centenary of his birth, ensured his place "not only in the history of medicine, but in every history of social endeavour".[17]

Breslau is now in Poland and is called Wroclaw. Neisser's house was bequeathed to the city and became an art gallery, the larger rooms being used for concerts. It was confiscated by the Nazis in 1933, turned into a guest house, and later destroyed during the second world war. Fortunately, his papers were salvaged and to this day are stored in the library of the hospital that he built.

References

1 Neisser A. Ueber eine der Gonorrhoe eigentumliche Micrococcusform. *Zentralblatt für die Medizinischen Wissenschaften* 1879;**17**:497–500.

2 Bumm E. *Der Micro-organismus der gonorrhoischen Schleimhaut-Erkrankungen "Gonococcus-Neisser"*. Wiesbaden: JF Bergmann, 1885.

3 Wertheim E. Reinzuchtung des Gonococcus Neisser mittels des Plattenverfahrens. *Dtsch Med Wochenschr* 1891;**17**:1351–2.

4 Hansen GA. Indberetning til det norske medicinske Selskap i Christiania om en med Understottelse av Selkabet foretage Reise for at anstille Undersogelser angaaende Spedalskhedens Aarsager. *Norsk Magazin for Laegevidenskaben* 1874;**9**:1–88. (Translated) Causes of leprosy. *International Journal of Leprosy* 1955;**23**:307–10.

5 Neisser A. Zur Aetiologie der Lepra. *Breslauer Artze Zeitschrift* 1879;**1**:200–2,214–5.

6 Hansen GA, Bacillus leprae. *Quarterly Journal of the Microscopical Science* 1880;**20**:92–102.

7 Neisser A. Weitere Beitrage zur Aetiologie der Lepra. *Virchows Archiv fur Pathologische Anatomie und Physiologie und fur Klinische Medizin* 1881;**84**:514–22.

8 Fite GL, Wade HW. The contribution of Neisser to the establishment of the Hansen bacillus as the aetiologic agent of leprosy and the so-called Hansen-Neisser controversy. *International Journal of Leprosy* 1955;**23**:418–27.

9 Richter JH. Albert Neisser. *Arch Dermatol* 1955;**71**:92–4.

10 Schadewaldt H. Neisser, Albert Ludwig Sigesmund. In: Gillispie CC, ed. *Dictionary of scientific biography*. New York: Charles Scribner, 1974:17–9.

11 Goldsmith WN. Breslau as I remember it. *Br J Dermatol* 1964;**76**:453–8.

12 Neisser A. Gonorrhoea: its dangers to society. *Medical News New York* 1900;**76**:41–5, 85–9.

13 Schmitz S. Albert Neisser. *Leben und Werk auf Grund neuer, unveroffentlichter Quellen*. Dusseldorf: Michael Triltsch 1968:44–8.

14 Metchnikoff E, Roux PPE. Etudes experimentales sur la syphilis. *Ann Inst Pasteur* 1903;**17**:809–21.

15 Metchnikoff E, Roux PPE. Etudes experimentales sur la syphilis. *Ann Inst Pasteur* 1904;**18**:1–6.

16 Gardner FT. In: Neisser A. *On modern syphilotherapy*. 1911. (Translated by IS Wartenberg). *Bulletin of the History of*

Medicine 1944;**16**:469–510.
17 Harrison LW. Neisser and neisserian principles in venereology. *British Journal of Venereal Diseases* 1955;**31**:65–73.
18 Neisser A. *Beitrage zur Pathologie und Therapie der Syphilis.* Berlin: Springer, 1911.
19 Schaudinn FR, Hoffmann E, Vorlaufiger Bericht uber das Vorkommen von Spirochaeten in syphilitischen Krankheitsprodukten und bei Papillomen. *Arbeiten aus dem K Gesundheitsamte* 1905;**22**:527–34.
20 Hecht H. Half a century of serodiagnosis of syphilis: discovery and development. *Arch Dermatol* 1956;**73**:426–40.
21 Wassermann A, Neisser A, Bruck C. Eine serodiagnostiche Reaction bei Syphilis. *Dtsch Med Wochenschr* 1906;**32**:745–6.
22 Wassermann A, Neisser A, Bruck C, Schucht A. Weitere Mitteilungen uber den Nachweis spezifischluetischer Substanzen durch Komplementverankerung. *Zeitschrift für Hygiene und Infektionskrankheiten* 1906;**55**:451–77.
23 Neisser A. The Cavendish lecture. The evolution of the modern treatment of syphilis. *West London Medical Journal* 1911;**16**:161–82.
24 Pusey WA. The history of dermatology. Springfield Illinois: Charles C Thomas, 1933:155–9.
25 Neisser A, Kuznitsky E. Ueber die Bedeutung des Ehrlich'schen Arsenobenzols fur die Syphilisbehandlung. *Berliner Klinische Wochenschrift* 1910;**47**:1485–90.
26 Jadassohn J. Albert Neisser 1855–1916. *Archiv für Dermatologie und Syphilis* 1916;**123**:17–64.
27 Anonymous. Obituary notice. *Lancet* 1916;ii:766.
28 Pinkus F. Albert Neisser. *Medical Clinics of Chicago (in North America)* 1916;**12**:914–6.
29 Scholz A, Sebastian G. Albert Neisser and his pupils. In: Herzberg JJ, Korting GW, eds. *On the history of German dermatology.* Berlin: Grosse, 1987:167–77.
30 Blaschko A. Albert Neisser. *Mitteilungen der deutschen gesellschaft zur Bekampfung der Geschlechtskrankheiten* 1916;**14**: 76–83.